REMARKS/ARGUMENTS

In response to the Office Action mailed August 5, 2009, Applicant amends his application and requests reconsideration. Claims 1-25 were originally pending in this application. Claims 1-10, 15-16, and 18-26 are cancelled, and claims 11-14, 17 and 27-28 are pending and undergoing examination.

Applicant acknowledges the Examiner's withdrawal of the objection to claims 13 and 15 in response to Applicant's amendments.

Applicant also acknowledges the Examiner's withdrawal of the rejections of claims 11-17 under 35 U.S.C. §112, second paragraph, after amending the claims to recite SEQ ID NO: 1.

Applicant gratefully acknowledges the Examiner's withdrawal of the rejection of claims 11-12 and 17, under 35 U.S.C. §102(b), in view of Applicant's amendment and response.

Claim Amendments

Applicant has amended claims 11, and 13-14, to clarify and further refine that which Applicant considers to be the invention. In particular, Applicant has amended the claims to clarify that the transplant support comprises a biopolymer having the thickness of approximately an average cornea (or approximately half of the thickness of an average cornea), and having the shape of a cornea, with a convex and concave side and suitable for implantation onto a damaged cornea, and the biopolymer having incorporated within it, an attachment reagent consisting essentially of one or more of the following compounds: laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, and EGF conjugated with polycarbophil. These claim amendments are fully supported by the specification, including, for example, at paragraphs [0014], [0026] and [0030]. No new matter has been added by these amendments.

Solely for the purpose of advancing prosecution of the instant application, Applicant has cancelled claims 15 and 16. Applicant reserves the right to reinstate these claims in a continuation or divisional application.

Discussion of the Obviousness Rejection

The Examiner has maintained the rejection of claims 11-17 under 35 U.S.C. §103(a), as unpatentable, over Parenteau et al., in view of USP 6,645,715 to Griffith et al., and USP 6,689,165 to Jacob et al. for the reasons made previously of record. Applicant traverses this rejection.

On page 6 of the Office Action, the Examiner indicates that the transitional phrase "consisting essentially of" is being interpreted as "comprising" because it is unclear to the Examiner what the basic and novel characteristics are of Applicant's claim.

Applicant has amended claims 11 and 13 to show that the claimed invention is directed a corneal transplant support comprising a base biopolymer having the thickness of approximately an average cornea (or half the thickness of an average cornea), and having the shape of a cornea, with a convex and concave side and suitable for implantation onto a damaged cornea; and the biopolymer having incorporated within it an attachment reagent consisting essentially of one or more of the following compounds: laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, and EGF conjugated with polycarbophil.

Applicant's Claimed Invention

Applicant is claiming a corneal transplant support, not an artificial cornea, as taught in Parenteau et al., or Griffith et al. Applicant's claims, as now amended, do not encompass a support having any cell types within the corneal support. The claimed support is suitable for growth of corneal endothelial cells and may also be suitable for growth of other corneal cells, so that they may be transplanted while on the support, to the damaged corneal region. However, what Applicant presently discloses and claims contains no stroma, epithelial cells or keratocytes.

More importantly, Applicant's claimed corneal support is shaped like a cornea, with a convex and concave side, and has the thickness of either an average cornea (human corneas are approximately 0.530 mm thick in the central zone), or half of the average thickness, or approximately 0.265 mm thick in the central zone. Applicant has included a reference article by Doughty, M.J. et al. as attachment A, which discusses the thickness of human corneas.

In addition, Applicant's biopolymer support has incorporated into it, an attachment reagent consisting essentially of at least one or more of the following compounds at a range of concentrations: laminin (0.1 μg/ml to 500 μg/ml in PBS), fibronectin (0.1 μg/ml to 500 μg/ml in PBS), RGDS (SEQ ID NO: 1) (0.1 μg/ml to 200 μg/ml in PBS), collagen type IV (1 μg/ml to 1000 μg/ml in 0.1 M acetic acid), collagen type I (1 μg/ml to 1000 μg/ml in 0.1 M acetic acid), bFGF conjugated with polycarbophil (1 ng/ml to 500 ng/ml in PBS conjugated with polycarbophil at about 0.1 μg/ml), and EGF conjugated with polycarbophil (1 ng/ml to 500 ng/ml in PBS conjugated with polycarbophil at about 0.1 μg/ml) (See Applicant's specification, *inter alia*, at paragraphs [0014], [0026] and [0030]). Other embodiments of Applicant's invention are directed to a biopolymer comprising collagen type IV and an additional coating of diamond-like carbon.

The Parenteau et al. Construct

Parenteau et al. has been discussed previously, however, Applicant wishes to clarify and point out certain distinctions in the teachings of the corneal equivalent of Parenteau et al. which have not been previously discussed, with that of Applicant's claimed invention.

The construction of the corneal equivalent (construct) in Parenteau et al. is nothing at all like what Applicant claims. The construct is discussed in detail at columns 5 and 6, and Figs. 11A to 11D of Parenteau et al. Parenteau et al. seed human corneal endothelial cells (HCEC) onto a polycarbonate insert which is porous and used to allow cells to get nutrients from media below the insert. Next, a collagen solution is added to the cell layer (col. 5, lines 40-60), with cell media and allowed to stay for 4 days. It is disclosed that the cell culture insert has an area of 2 cm^2 and 1 ml of collagen is added. Thus, in at least this embodiment, the collagen "biopolymer"

layer taught in Parenteau et al. is approximately 0.5 cm thick. A layer 0.5 cm thick is equivalent to 5000 μm thick, which is 10 times the thickness of the average full-thickness cornea.

Continuing on, Parenteau et al. teach that the next step is preparing a collagen mixture which contains keratocytes to make a mixture having about 100 keratocytes per μg of collagen. This mixture is then added to the same cell culture insert and forms a raised area of 2.5 cm^2 (col. 6, lines 42-60, col. 7, lines 8-32).

The final step in Parenteau et al. is the seeding of epithelial cells onto the surface and allowed to grow over the collagen-keratocyte mixture layer.

There is no teaching in Parenteau et al. of a corneal transplant support, comprising a biopolymer having the shape and the thickness of a cornea, which has incorporated into it, an attachment reagent consisting essentially of one or more of the following compounds: laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, and EGF conjugated with polycarbophil, which is suitable for endothelial cell growth as disclosed and claimed by Applicant.

The Griffith et al. Construct

The construction of the corneal equivalent in Griffith et al. is similar to Parenteau et al. Cells from the endothelium, stroma and epithelium, are taken from a donor and separated and cultured and immortalized for use as cell lines (Griffith et al., col. 7, lines 5 to 65). The growing cells were then screened for correct morphology.

The next step comprises adding trypsinized corneal endothelial cells to a cell culture insert which may be coated with collagen. After growing to 80% confluence, a second layer of collagen and fibronectin is added on top of the endothelial cells, followed by another layer which is a mixture of keratocytes and collagen and chondroitin sulphate. This continues until an epithelial cell layer is eventually added (col. 12, lines 7 to 55).

As with Parenteau et al., nowhere in Griffith et al. is there any teaching of Applicant's corneal transplant support, comprising a biopolymer having the shape and the thickness of a cornea, which has incorporated into it, an attachment reagent

consisting essentially of one or more of the following compounds: laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, and EGF conjugated with polycarbophil, which is suitable for endothelial cell growth.

Discussion of Jacob et al.

It is important for the Examiner to understand the teaching of Jacob et al., so as to understand why one of ordinary skill in the art, at the time the Applicant's invention was made, would not have looked to Jacob et al., because Jacob et al. actually teaches away from Applicant's claimed invention.

To begin, Jacob et al. give a summary of the wound healing art and discuss the knowledge that certain growth factors are important in healing and may be useful in corneal epithelial repair (See, paragraphs [0005]-[0018] of Jacob et al.).

Jacob et al. teach that proteins and growth factors, when adsorbed or otherwise adhere to synthetic polymers or other surfaces, have interactions with the synthetic or polymer surfaces which can cause minor denaturation or conformational changes in these proteins and growth factors (Jacob et al. at paragraph [0021]). In addition, it is taught that different biological responses can occur with different synthetic materials because the resulting protein layer interaction can be different in each case (Jacob et al. at paragraph [0023]).

Jacob et al. then discuss the use of short peptides as molecules that may help cell adhesion. However, it is taught that the use of RGD on hydrogels for growing rabbit corneal epithelial cells was not very efficient, and in some cases, actually inhibited cell growth and migration (Jacob et al. at paragraph [0031]).

These teachings are followed by a discussion of the prior art indicating that attaching a peptide to a surface with a spacer are covalently, increased the cellular response. Furthermore, tethering growth factors by covalently linking them to a polyethylene oxide molecule (PEO) significantly increased cell adhesion on the polymer surface (Jacob et al. at paragraphs [0032]-[0033]).

In addition, Jacob et al. point out that corneal epithelial cells appear to recognize polymer surfaces as "non-self" and trigger immune rejection (Jacob et al. at

paragraph [0044]). Thus, Jacob et al. hypothesized that if growth factors could be tethered covalently to a polymer, the tether would keep the growth factors far enough away from the polymer surface to prevent non-specific binding, and increase cell adhesion (Jacob et al. at paragraph [0045]).

As such, Jacob et al. teach that when one of ordinary skill in the art is using a polymer substrate to grow corneal epithelial cells, the growth factors must be tethered or otherwise covalently bound to the polymer via a linear polyethylene oxide (PEO) molecule, or amino acid or peptide, with a molecular weight between 2000-8000.

Therefore, one of ordinary skill in the art, would understand that Jacob et al. teach away from Applicant's claimed invention, in which the biopolymers are embedded or incorporated into the surface using adsorption or ionic interaction, in the complete opposite way from the method disclosed in Jacob et al.

For subject matter defined by a claim to be considered obvious, the Office must demonstrate that the differences between the claimed subject matter and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on certain factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art, and (4), objective evidence of nonobviousness. *Graham*, 3838 U.S. at 17-18, 148 USPQ at 467.

Consideration of the aforementioned Graham factors here indicates that the present invention, as defined by the amended claims, is unobvious in view of specification and claims of the present patent application.

With regard to the differences between the cited references and Applicant's invention in view of the amended claims, Applicant submits that none of these references, alone or in combination, teaches a biopolymer in the shape and thickness of an average cornea (or half the average thickness), having a concave and convex side, and having growth and attachment factors consisting essentially of one or more

of the following compounds: laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, and EGF conjugated with polycarbophil, incorporated *within* the biopolymer, that is suitable for transplantation into a damaged cornea, as now claimed by Applicant. Parenteau et al. was discussed above. As stated previously, Griffith et al. teach an *in-vitro*, avascular, human corneal equivalent, comprising immortalized human cell lines, not a corneal biopolymer support as claimed by Applicant, suitable for transplant into a cornea (abstract, col.7 – col. 8).

Furthermore, nowhere in Griffith et al. is there any teaching of Applicant's corneal transplant support, comprising a biopolymer having the shape and the thickness of a cornea, which has incorporated into it, an attachment reagent consisting essentially of one or more of the following compounds: laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, and EGF conjugated with polycarbophil, which is suitable for endothelial cell growth.

As stated previously, Jacob et al. teach an ocular device comprising an optical polymer having biocompatible linear, single chain tether molecules having two ends, attached to the optical polymer on one end of the tether, and a corneal enhancer molecule or growth factor attached to the tether at the other end. Jacob et al. also teach that when one of ordinary skill in the art is using a polymer substrate to grow corneal epithelial cells, the growth factors must be tethered or otherwise covalently bound to the polymer via a linear polyethylene oxide (PEO) molecule, or amino acid or peptide,, with a molecular weight between 2000-8000. Applicant's claimed support does not use any such chemical modifications. More importantly, Jacob et al. teach away from the attachment reagent claimed by Applicant, because Jacob et al. teach that the use of RGD on hydrogels for growing rabbit corneal epithelial cells was not very efficient, and in some cases, actually inhibited cell growth.

Considering all of the Graham factors together, it is clear that the Applicant's invention, as now presently claimed, would not have been obvious to one of ordinary skill in the art, at the relevant time, in view of the prior art references. Applicant submits that the combination of teachings of Parenteau et al., in view of Griffith et al. and Jacob et al., do not teach each and every feature of Applicant's claimed invention.

A rationale to support a conclusion that a claim would have been obvious requires that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 US 398, 408, 82 USPQ2d 1385, 1395 (2007).

The Court in *KSR* noted that obviousness cannot be proven merely by showing the elements of a claimed device were known in the art; it must be shown that those of ordinary skill in the art would have had some "apparent reason" to combine the known elements in the fashion claimed. *KSR* at 1741. In the same way, when the prior art teaches away from the claimed invention, as shown in Appellant's arguments and other objective evidence, obviousness cannot be proven by merely showing that the biopolymer composition and growth factors were known, and corneal endothelial cells could be modified by routine experimentation. See, *Ex parte Whalen* II, Appeal 2007-4423, (BPAI July 23, 2008) at pp. 13-16.

Applicant submits that one of ordinary skill in the art, in an attempt to make an artificial corneal transplant support, would not have looked to Parenteau et al., in view of Griffith et al., and Jacob et al., because both Parenteau et al. and Griffith et al. teach entire corneal constructs including stroma and epithelial cells, not Applicant's biopolymer support. Moreover, neither of these references teach anything about a corneal transplant support comprising a biopolymer in the shape of a cornea, having a concave and convex side, having the thickness of an average cornea (or half the thickness), and having growth and attachment factors consisting essentially of one or more of the following compounds: laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, and EGF conjugated with polycarbophil, incorporated *within* the biopolymer, that is suitable for transplantation into a damaged cornea, as now claimed by Applicant. The methods and reagents used to grow the different cell types in the cited references are not applicable to Applicant's claimed invention.

Further, one of ordinary skill in the art would understand in Applicant's invention, the combination of attachment factors, do not have to be covalently bound,

as in Jacob et al., but only mixed into the polymer, to be effective. Applicant's claimed method is simpler, and more effective and less costly, as there are no synthesis steps for making the tethered growth factors. Moreover, Jacob et al. actually teach away from the use of RGD, which is a component of Applicant's claimed attachment reagent, on hydrogels for corneal epithelial cells.

Applicant submits that the combination of Parenteau et al., in view of Griffith et al. and Jacob et al. does not make Applicant's claimed invention *prima facie* obvious, because: 1) the combination of references does not teach each and every element of Applicant's claimed invention, namely, the combination of references does not teach a corneal transplant support consisting essentially of a biopolymer in the shape of a cornea, having a concave and convex side, and having the thickness of an average (or half the average) cornea, and having growth and attachment factors consisting essentially of one or more of the following compounds: laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, and EGF conjugated with polycarbophil, incorporated *within* the biopolymer, that is suitable for transplantation into a damaged cornea; and 2) the combination of references teaches away from Applicant's invention, because the primary reference of Parenteau et al. and Griffith et al. are directed to constructs containing cells immortalized human corneal endothelial cells (not cells from a patient's cornea), and the secondary reference of Jacob et al. teaches away from Applicant's claimed invention, because it teaches that growth factors must be covalently bound, or teathered to the biopolymer to work, and teaches that RGD is not suitable as an attachment reagent on hydrogels for corneal epithelial cells.

Applicant has discussed the teachings of each cited reference, and then has shown that when the *combination of references* is considered, the *combination* of teachings cannot render Applicant's claimed invention, *as a whole*, *prima facie* obvious, because the combination of teachings do not encompass all of Applicant's claimed features, and because the combination of teachings teach away from Applicant's claimed invention. As such, Applicant respectfully requests withdrawal of this rejection.

Conclusion

Applicant respectfully submits that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Date: December 8, 2009

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ATTACHMENT A

Patient Research Beta

Elsevier is the world's leading publisher of Medical Information. We are proud to make available our Patient Research option as a Beta program for patients, or friends/family of patients, who have a medical need for information regarding a medical situation for them or someone they know. This Beta program provides the article you request for free, with a small handling fee, $4.95. After ordering the article and confirmation of payment, we will e-mail the document to you typically within 2 hours, but no longer than 24 hours.

Human Corneal Thickness and Its Impact on Intraocular Pressure Measures*1, *2A Review and Meta-analysis Approach

Survey of Ophthalmology, Volume 44, Issue 5, March-April 2000, Pages 367-408

Michael J. Doughty PhD, and Mohammed L. Zaman MBBS.

Abstract: We determined the "normal" central corneal thickness (CCT) value in human corneas based on reported literature values for within-study average CCT values, and used this as a reference to assess the reported impact of physiological variables (especially age and diurnal effects), contact lens wear, pharmaceuticals, ocular disease, and ophthalmic surgery on CCT. With the expected CCT and its variance defined, it should be possible to determine the potential impact of differences in CCT in intraocular pressure (IOP) assessments, especially by applanation tonometry, using a meta-analysis approach. Some 600 sets of CCT data were identified from the worldwide literature over the period of 1968 through mid-1999, of which 134 included IOP measures as well. The within-study average CCT values and reported variance (SD) was noted along with the number of eyes and any special characteristics, including probable ethnic origin of the study subjects. Various sets of data were subjected to statistical analyses. From 300 data sets from eyes designated as normal, the group-averaged CCT was 0.534 mm. From 230 data sets where interindividual variance was reported, the group-averaged CCT was 0.536 mm (median 0.536 mm; average SD of 0.031 mm, average coefficient of variation = 5.8%). Overall, studies using slit-lamp-based pachometry have reported marginally lower CCT values (average 0.530 mm, average SD 0.029 mm) compared to ultrasound-based studies (average 0.544, average SD 0.034 mm), which perhaps reflects the type of individual studied (non-surgical vs. pre-surgical patients) rather than the technique itself. A slight chronological increase in reported average CCT values (approximately 0.006 mm/decade) was evident, but a substantial chronological increase was evident for ultrasound pachometry studies (approximately 0.015 mm/decade). Within the meta-analysis-generated average and variance, age had no obvious impact on CCT measures for *whites, although an age-related decline in CCT is evident for non-whites. Any diurnal effects are likely concealed within the expected variance in CCT. Contact lens wear and pharmaceuticals generally produced changes in CCT that were well within the expected variance in CCT. Of the ocular diseases, only those associated with collagen disorders (including keratoconus) or endothelial-based corneal dystrophies (e.g., Fuchs) were likely to result in decreases or increases, respectively, of CCT beyond the normal variance. Routine contact lens wear and diseases such as diabetes seem unlikely to produce changes in CCT of a magnitude that would justify pachometry as a monitoring method beyond routine slit-lamp evaluation. Increases in CCT beyond

the expected variance were reported after a range of intraocular surgeries (cataract operations, penetrating keratoplasty), whereas photorefractive surgery produces a measurable decrease in CCT. A meta-analysis of possible association between CCT and IOP measures of 133 data sets, regardless of the type of eyes assessed, revealed a statistically significant correlation; a 10% difference in CCT would result in a 3.4 ± 0.9 mm Hg difference in IOP ($P \leq 0.001$, $r = 0.419$). The observed phenomenon was much smaller for eyes designated as healthy (1.1 ± 0.6 mm Hg for a 10% difference in CCT, $P = 0.023$, $r = 0.331$). For eyes with chronic diseases, the change was 2.5 ± 1.1 mm Hg for a 10% difference in CCT ($P = 0.005$, $r = 0.450$), whereas a substantial but highly variable association was seen for eyes with acute onset disease (approximately 10.0 ± 3.1 mm Hg for a 10% difference in CCT, $P = 0.004$, $r = 0.623$). Based on the meta-analysis, normal CCT in white adults would be expected to be within ±11.6% (±2 SD) of 0.535 mm, i.e., 0.473–0.597 mm (95% CI, 0.474–0.596). The impact of CCT on applanation tonometry of healthy eyes is unlikely to achieve clinical significance, but for corneas of eyes with chronic disease, pachometry should be performed if the tonometry reveals IOP readings that are borderline or unusual. The meta-analysis confirms that, for these eyes, low CCT values can result in low tonometry readings and high CCT values can result in elevated tonometry readings. The correction for eyes with chronic disease should be 2 or 3 mm Hg for a 0.05-mm difference in CCT from 0.535 mm. It is unknown whether this same correction should be specifically applied to the elderly, especially in non-whites.